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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KAROL, JODY LYNN	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/505,137	BHATARAH ET AL.	
	Examiner	Art Unit	
	JODY L. KAROL	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/21/2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *77-106* is/are pending in the application.

4a) Of the above claim(s) *81,99-103 and 106* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *77-80,82-98,104 and 105* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the Response to Election/Restriction filed on 12/21/2007. No claims have been amended and no new claims have been added. Accordingly, claims 77-106 are currently pending in the application.

Election/Restrictions

1. Applicant's election **with** traverse of Group I, claims 77-103, drawn to a method for preparing a sterile pharmaceutical composition of a steroid, and the species election **with** traverse of budesonide in the reply filed on 12/21/2007 is acknowledged. In view of Applicant's arguments, the restriction requirement is herein withdrawn. However, Applicant's arguments with respect to the species election have been fully considered but have not been found persuasive.

The traversal of the election of species is on the grounds that there is not a search burden because the subject matter of species I (budesonide) would necessarily overlap with a search for the subject matter of species II (fluticasone). While budesonide and fluticasone are both steroids, the Examiner respectfully points out that budesonide is a classified as glucocorticosteroid, and fluticasone as a corticosteroid. Furthermore, the species are structurally different, would require different searches, and are not obvious variants of each other based on the current record.

The election of species requirement is still deemed proper and is therefore made FINAL.

Claims 81, 99-103 and 106 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Accordingly, claims 77-80, 82-98 and 104-105 are examined on the merits herein.

Priority

2. Acknowledgement is made of Applicant's claim for foreign priority based on Applications No. 0218724.3 and 0203912.1 filed in the United Kingdom on 8/24/2002 and 2/19/2002 respectively.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 104-105 rejected under 35 U.S.C. 102(b) as being clearly anticipated by Karlsson et al. (WO 99/25359). See MPEP § 2173.05(c).

The Examiner notes that claims 104-105 are product-by-process claims. From MPEP § 2113: "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art,

the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Karlsson et al. teaches sterile pharmaceutical formulations comprising budesonide in aqueous suspension (see page 8, lines 4-6, and pages 14-15, Examples 4-5). Therefore, all the limitations of claims 104-105 are clearly met.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.,* 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 77-80, and 82-98 rejected under 35 U.S.C. 103(a) as being unpatentable over Harris et al. (US 6,187,765 B1).

The instant claims are directed to methods for preparing sterile pharmaceutical compositions of the steroid, budesonide, comprising dissolving the non-sterile steroid in a solvent to yield a solution of the steroid; filtering the solution to yield a sterile solution; combining the sterile solution with sterile water to form a suspension; optionally removing all or part of the solvent; treating the suspension to obtain a particle size distribution having a mass median diameter less than 10 μm; under sterile conditions combining said suspension with a pharmaceutically acceptable carrier to yield a sterile composition; and storing said composition in a sterile container.

Harris et al. teaches aqueous suspensions of water-insoluble pharmaceutical substance intended for inhalation therapy (see column 1, lines 12-15). Harris further teaches in Example 1, a method of preparing a sterile suspension of a steroid, mometasone furoate, comprising dissolving said steroid in acetone, a class 3 solvent as claimed in the instant claim 83; filtering said solution through a sterilizing filter, such as a filtration medium having pore sizes not exceeding 0.2 μm in diameter, as claimed in the instant claims 89 and 96, into a sterile vessel; heating said sterile solution to about 45-50 °C and slowly adding sterile purified water over 15 min.; while maintaining the

temperature and more of the sterile water and stir for 30 min.; continuing to maintain the temperature and stir for another 30 min. during which a precipitate forms; slowly adding more water and stirring for 60 min. at the elevated temperature; stirring at 60 min. at the elevated temperature; cooling the mixture to ambient temperature while stirring; filtering said precipitate and washing with water; and drying under vacuum to yield dry sterile mometasone furoate (see column 6, lines 25-62). The sterile mometasone furoate is then added to a sterile carrier solution comprising polysorbate (a surfactant) as claimed in the instant claim 90, to form a suspension; said suspension is passed through a Microfluidizer to yield a suspension with a median particle size of 1.24 as claimed in the instant claims 91 and 97 (see column 7, lines 65-68); and the sterile suspension is transferred to sterile containers for use in a nebulizer (i.e. an ampoule as claimed in the instant claim 93) (see column 6, line 64 to column 7, line 36).

Harris et al. does not teach a method of preparing a sterile suspension of steroid where the steps are in the same order as claimed. For example, Harris et al. teaches the sterile suspension is combined with a carrier before the suspension is treated to obtain the desired particle size, which is opposite to what is claimed. However, it has been held that merely reversing the order of steps in a multi-step process is not a patentable modification absent unexpected or unobvious results. *Ex Parte Rubin*, 128 USPQ 440 (Bd. App. 1959). See also *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946).

Harris et al. additionally teaches extra steps, such as isolating and drying the steroid. However, the term "comprising" is interpreted as broad and open, and the extra steps taught by Harris et al. are not excluded by the claim language.

Harris et al. also does not teach a method for preparing a sterile suspension of steroid wherein the steroid is budesonide. However, Harris et al. does teach that aqueous suspensions of drug particles for nebulization are known, and mentions budesonide as a commercially available product (see column 2, lines 5-12). Harris et al. also teaches that formulations that are to be inhaled must be free of pathogenic organisms, and thus be prepared and handled under sterile conditions (see column 3, lines 7-10). It would have been obvious to one of ordinary skill in the art to substitute budesonide for mometasone furoate as the steroid in the method taught by Harris et al., to produce a sterile suspension of budesonide. One of ordinary skill in the art would have been motivated to do so in order to produce an inhalable formulation of budesonide free of any potential pathogenic organisms.

In regards to the instant claims 78-79, wherein the budesonide steroid is a powder or micronized power, Harris et al. does not explicitly teach using a powder steroid, or a micronized powder sterile to prepare the sterile suspensions. However, it would have been obvious to one of ordinary skill in the art at the time of invention to use a powder or micronized powder of the steroid to prepare the sterile suspensions because powders and micronized powders have an increase surface area. One of ordinary skill in the art would have been motivated to increase the surface area of the steroid to increase the rate at which the steroid dissolves in the solvent.

In regards to claims 82, 84, and 95, Harris et al. does not teach dissolving the steroid in alcohol or a class 2 solvent. Harris et al. teaches dissolving the steroid in acetone (as described *supra*). However, it is been held that the selection of a known material based on its suitability for its intended use supported a *prima facie* case of obviousness determination in *Sinclair & Carroll Co. V. Interchemical Corp.*, 325, US 327, 65 USPQ 297 (1945). Accordingly, since alcohol and class 2 solvents are known solvents, it would have been obvious to one or ordinary skill in the art at the time of the invention to select an appropriate solvent to dissolve the steroid.

In regards to the instant claim 85-86, the boiling point of acetone is 56.5°C. Harris et al. teaches dissolving the steroid at 45-50°C which is significantly overlaps with the range as claimed in the instant claim 85. Harris et al. does not teach adding the steroid to the solvent wherein the solvent is at reflux. However, it would have been obvious to one of ordinary skill in the art at the time of the invention to add the steroid to the solvent at reflux. One of ordinary skill in the art would have been motivated to do so to increase the rate at which the steroid dissolves in said solvent.

In regards to claims 87, Harris et al. does not teach removing the solvent under reduced pressure. Acetone (the solvent taught by Harris et al.) will evaporate on its own at room temperature to a certain extent. Heating any solvent or reducing the pressure any solvent is kept at, will increases the rate at which the solvent evaporates. Harris et al. heats the acetone (see column 6, lines 37-40). Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to remove the

solvent under reduce pressure. One of ordinary skill in the art would have been motivated to do so to increase the rate of solvent removal.

In regards to the instant claims 92 and 98, Harris et al. does not explicitly teach steroid particles in the suspension having a mass median diameter in the range of 2-3 μm. However, Hara et al. does teach that the preferred average particle size for inhaled particles is 0.5 to 5 μm (see column 1, lines 27-43 and column 2, lines 65-67). Furthermore, Harris et al. claims suspensions where the particle size is less than 5 μm, which significantly overlaps with range as claimed (see column 10, claim 14), and teaches suspensions where the median particle size is 1.24 μm. In this case, where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 UPSQ 90 (CCPA 1976). Furthermore, while the references do not explicitly teach the claimed particle size range, it is the Examiner's opinion that the determination of optimal or workable particle size range by routine experimentation is obvious absent showing of criticality of the claimed particle size range. One having ordinary skill in the art would have been motivated to do this to obtain an optimal particle size for inhaled steroids.

Therefore, the invention as a whole would have been *prima facie* obvious to one skilled in the art at the time it was made.

Conclusion

No claims are allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JODY L. KAROL whose telephone number is (571)270-3283. The examiner can normally be reached on 8:30 am - 5:00 pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

JLK

/SREENI PADMANABHAN/
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